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High-Sensitivity Troponin T, NT-proBNP and Glomerular Filtration Rate: a Multimarker Strategy for Risk Stratification in Chronic Heart Failure

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Short title: Biomarkers and prognosis in heart failure

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Abstract

Background: High-sensitivity troponin T (hs-TnT) emerged as a robust predictor of prognosis in stable chronic heart failure (HF) in an individual patient data meta-analysis. In the same population, we compared the predictive performances of hs-TnT, pro-B-type natriuretic peptide N-terminal fraction (NT-proBNP), hs-C-reactive protein (hs-CRP), and estimated glomerular filtration rate (eGFR).

Methods and Results: 9289 patients (66±12 years, 77% men, 85% LVEF <40%, 60% ischemic HF) were evaluated over a 2.4-year median follow-up. Median eGFR was 58 mL/min/1.73 m^2 (interquartile interval 46-70; n=9220), hs-TnT 16 ng/L (8-20; n=9289), NT-proBNP 1067 ng/L (433-2470; n=8845), and hs-CRP 3.3 mg/L (1.4-7.8; n=7083). In a model including all 3 biomarkers, only hs-TnT and NT-proBNP were independent predictors of all-cause and cardiovascular mortality and cardiovascular hospitalization. hs-TnT was a stronger predictor than NT-proBNP: for example, the a risk for all-cause death increased by 54% per doubling of hs-TnT vs. 24% per doubling of NT-proBNP. eGFR showed independent prognostic value from both hs-TnT and NT-proBNP. The best hs-TnT and NT-proBNP cut-offs for the prediction of all-cause death increased progressively with declining renal function (eGFR ≥90: hs-TnT 13 ng/L and NT-proBNP 825 ng/L; eGFR <30: hs-TnT 40 ng/L and NT-proBNP 4608 ng/L). Patient categorization according to these cut-offs effectively stratified patient prognosis for the 3 endpoints across all eGFR classes.

Conclusions: hs-TnT conveys independent prognostic information from NT-proBNP, while hs-CRP does not. Concomitant assessment of eGFR may further refine risk stratification. Patient classification according to hs-TnT and NT-proBNP cut-offs specific for the eGFR classes holds prognostic significance.

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Introduction

Heart failure (HF) is a highly prevalent disease condition, and a leading cause of morbidity and mortality worldwide.[1] Accurate risk prediction allows to tailor HF treatment and follow-up strategy in the individual patient, possibly resulting in better quality of life and long-term prognosis.[2] Many predictors of death and/or HF-related hospitalization have been identified, although their applicability in common clinical practice is often limited, and precise risk stratification in HF remains challenging.[2]

Cardiac biomarkers are gaining increasing recognition as tools for risk prediction in HF.[3] In particular, the American Heart Association/American College of Cardiology Foundation has issued a class I, level of evidence A recommendation for the assessment of B-type natriuretic peptide (BNP) or the N-terminal fraction of pro-BNP (NT-proBNP) for prognostic stratification in chronic HF.[4] Furthermore, troponin elevation is a frequent finding in chronic HF, and has been established in several studies as a predictor of adverse outcome.[5] In a recent meta-analysis concerning 9289 individual patient data (IPD) from 11 cohorts, we confirmed a strong prognostic value of high-sensitivity (hs) TnT assay for all-cause death, cardiovascular death, and cardiovascular hospitalization, additive to established risk markers (sex, age, ischemic vs. non-ischemic etiology, left ventricular ejection fraction - LVEF, estimated glomerular filtration rate - eGFR, and also NT-proBNP). [6]

The mechanisms leading to the production and release of natriuretic peptides in HF include hemodynamic overload and neurohormonal activation, while troponin elevation is driven by ongoing cardiomyocyte necrosis/apoptosis.[7] Other biomarkers could contribute to refine risk stratification: in particular, a subclinical myocardial inflammation is frequently observed in HF and hs-C-reactive protein (hs-CRP) carries prognostic significance in chronic HF.[8-10] Furthermore, chronic kidney disease is a common comorbidity in chronic HF, with an established prognostic value in HF,[11, 12] and its presence is easily detectable by the estimated glomerular filtration rate (eGFR).

We felt it worthwhile to compare the prognostic performances of NT-proBNP, hs-TnT, hs-CRP, and eGFR, and to evaluate a multi-biomarker strategy for risk stratification in chronic HF in the largest IPD database currently available.

Methods

Search study, study selection

The design and main results of our IPD meta-analysis on hs-TnT in CHF have been reported in detail.[6] Briefly, in April 2017, two authors (AA and GV) independently searched 4 databases (Medline, EMBASE, Cochrane Library, and Scopus), using the following search terms: "troponin" AND "heart failure" OR "cardiac failure" OR "cardiac dysfunction" OR "cardiac insufficiency" OR "left ventricular dysfunction". The inclusion criteria were: English language; patients aged ≥18 years and diagnosed with HF; reported enrolment of outpatients or patients undergoing elective admission; reported use of a hs-TnT and/or I assay; information on patient prognosis; authors' availability to provide IPD data. These last corresponded to as many as possible of the following variables: age, sex, ethnic group, body-mass index, comorbidities (hypertension, atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease), plasma hemoglobin, HF etiology (ischemic vs. non-ischemic), LVEF, hs-TnT and/or I, NPs, serum creatinine, hs-CRP), follow-up duration, and outcome measures (all-cause death, cardiovascular death, and hospitalization for cardiovascular cause).[6]

Ten studies met all these requirements, reporting data on 11 cohorts, with a total patient number of 9289.[13-22] Since hs-TnI values were available for a small minority of patients,[8] only hs-TnT was considered. Five other studies, including a total patient number of 1312, could not be included because of lack of IPD.[10,23-26]

Statistical analysis

For the present analysis, the IBM SPSS Statistics (version 22, 2013) and R statistical software (http://www.r-project.org/, version 3.4.0) were used. Normal distribution was assessed through the Kolmogorov-Smirnov test; variables with normal distribution were presented as mean±standard deviation, while those with non-normal distribution as median and interquartile interval. Mean differences among groups were evaluated through the unpaired Student T test. Pearson's product moment correlation coefficient (r) was calculated as a measure of linear association between normally distributed variables.

For all the following analyses, NT-proBNP, hs-TnT, hs-CRP, and eGFR were $\log_2$-transformed to account for non-normal distribution. Pearson's product moment correlation coefficient quantified the strength of correlation between normally distributed variables. Categorical variables were compared by the Chi-square test with Yates correction. The log-rank test (Mantel-Cox) was used to compare survival times on Kaplan-Meier curves. The optimal cut-offs for ROC curves were established by Youden's J statistic. At discrimination analysis, the AUC values were compared through the De Long's test. The D'Agostino-Nam version of the Hosmer-Lemeshow calibration test was used to calculate χ^2 values as measure of calibration. The net reclassification improvement (with risk categories set at <10%, 10-30% and >30%) and the integrated discrimination improvement were calculated to assess reclassification. Univariate and multivariate Cox regression analyses allowed to identify predictors of outcome. Multicollinearity (i.e. interference among variables included into a multivariable prognostic model) was assessed by calculating the Variance Inflation Factor (VIF). The Fine-Gray model was used to account for mutually exclusive endpoints; non-cardiovascular death was considered as competing risk for cardiovascular death, and all-cause death as competing risk for cardiovascular hospitalization.[27] p values <0.05 were considered significant.

Results

Patient population

The main characteristics of the 9289 patients, divided into their cohorts, are reported in **Table 1.** Overall, patients were aged 66±12 years, and were more often males (n=7122, 77%). The majority of patients had HF with reduced ejection fraction (LVEF <40%: n=7902, 85%; LVEF 40-49%: n=718, 8%; LVEF ≥50%: n=479, 5%). All patients had available data on HF etiology; ischemic HF was more common (5543 patients, 60%). GFR, estimated from serum creatinine through the chronic kidney disease epidemiology collaboration (CKD-EPI) equation,[28] was available for 9220 patients (99%); its median value was 58 mL/min/1.73 m^2 (interquartile interval 46-70); patients on dialysis were not included in the original studies. Median follow-up duration was 2.4 years (interquartile interval 1.6-3.3). Data on all-cause death were available for all cohorts (2620 deaths, 28%), whereas data on cardiovascular death were available for 6 cohorts (8487 patients, 1725 events, 20%), and data on cardiovascular hospitalization for other 6 (8168 patients, 2375 events, 29%) (**Table 1**). At 1 year, 888 all-cause deaths (10%), 676 (7%) cardiovascular deaths, and 343 (4%) cardiovascular hospitalizations were recorded; at 5 years, these events were 2423 (26%), 1658 (18%), and 2244 (24%), respectively.

Circulating biomarker levels

NT-proBNP levels were available for 8845 patients (95%; median 1067 ng/L, interquartile interval 433-2470 ng/L). All patients had hs-TnT measured. In all studies was used the only available hs-TnT assay (Roche Diagnostics®, Basel, Switzerland; lower detection limit of 3 ng/L, 99^{th} percentile value in apparently healthy individuals of 14 ng/L).[29] Median value was 16 ng/L, with 8-20 ng/L interquartile interval. Finally, 7083 patients (83%) had hs-CRP data (median 3.3 mg/L, interquartile interval 1.4-7.8 mg/L).

Biomarkers and prognosis

When performing a comparative assessment of the prognostic performance of hs-TnT and other biomarkers, we found first that hs-TnT displayed higher AUC values than NT-proBNP for all 3

endpoints (all p values <0.001; **Figure 1**). Adding hs-TnT to NT-proBNP resulted in better discrimination and reclassification, compared to NT-proBNP alone, with a change in risk category in 28% of patients (**Supplemental Table 1**). These findings were confirmed in several population subsets (**Supplemental Table 2**). Adding hs-CRP to hs-TnT and NT-proBNP did not further improve risk prediction, compared to hs-TnT plus NT-proBNP (**Supplemental Table 1**).

NT-proBNP, hs-TnT and hs-CRP were univariate predictors of outcome, but only NT-proBNP and hs-TnT remained independent predictors in a model including all 3 biomarkers (**Table 2**). hs-TnT emerged as a stronger predictor of the 3 endpoints: for example, the risk for all-cause death increased by 54% per doubling of hs-TnT vs. 24% per doubling of NT-proBNP (**Table 2**). These findings were replicated across patient subgroups, categorized according to sex, age (≥ or <66 years), etiology (ischemic or non-ischemic), LVEF (<40%, 40-49%, ≥50%), and eGFR (<30, 30-59, 60-89, ≥90 mL/min/1.73 m^2) (**Supplemental Table 3**).

hs-TnT, NT-proBNP, renal function, and prognosis

In a model including NT-proBNP and hs-TnT, eGFR was independent predictor of both all-cause (HR 0.72, 95% CI 0.65-0.81; p<0.001) and cardiovascular death (HR 0.76, 95% CI 0.67-0.86; p<0.001), but not of cardiovascular hospitalization (HR 0.97, 95% CI 0.87-1.08; p=0.591). The variables displayed significant correlations (**Supplemental Table 4**), but multicollinearity was excluded because of VIF=1.15 (reference value <10).[30]

The best hs-TnT and NT-proBNP cut-offs for the prediction of the 3 endpoints increased with declining renal function (**Table 3**). At Kaplan-Meier analysis, patient classification according to these cut-offs proved effective in risk stratification across all eGFR categories. At baseline, hs-TnT and NT-proBNP were either both <cut-off or ≥cut-off in the majority of patients; these groups had the longest and the shortest survival, respectively (**Figures 2-4**), while discordant cases had an intermediate prognosis, with no significant differences between the two combinations (**Supplemental Tables 5** and **6**).

Discussion

In the largest cohort of patients with chronic HF so far assessed with this respect, NT-proBNP, hs-TnT, and hs-CRP were univariate predictors of all-cause death, cardiovascular death, and cardiovascular hospitalization. Furthermore, hs-TnT appeared a stronger predictor of outcome than NT-proBNP, based on both HR and AUC values. hs-TnT had also independent prognostic value from NT-proBNP, while hs-CRP did not. Adding hs-TnT to NT-proBNP resulted in better discrimination and reclassification compared with NT-proBNP alone, with a change in risk category for substantial percentages of patients (all-cause death: 28%, cardiovascular death: 24%, and cardiovascular hospitalization: 26%). The combination of hs-CRP, hs-TnT and NT-proBNP did not further improve risk stratification over hs-TnT plus NT-proBNP. On the other hand, eGFR was independent predictor of all-cause and cardiovascular mortality in a model including NT-proBNP and hs-TnT. The best hs-TnT and NT-proBNP cut-offs for the prediction of all-cause death increased with decreasing eGFR, and patient classification according to these cut-offs proved effective in risk stratification across all eGFR categories.

These results add to our previous report of an incremental prognostic value of hs-TnT, compared to a prognostic model including NT-proBNP (together with patient age, sex, ischemic etiology, LVEF, eGFR).[6] Interestingly, the same conclusions apply to patients with either ischemic or non-ischemic etiologies, confirming the established notion that the correlates of HF progression are broadly similar after an ischemic or non-ischemic cardiac insult. Similarly, no differences were found across age groups, and there was no interaction with patient sex, although women with HF tend to have lower natriuretic peptides levels, and also lower troponin concentration.[31] Finally, despite the wide heterogeneity in disease mechanisms and clinical presentation, hs-TnT retained an additive prognostic value to NT-proBNP across all categories of systolic dysfunction, namely in the <40% and 40-49% LVEF intervals, as well as among patients with preserved systolic function (LVEF ≥50%), reasonably because the disease mechanisms explored are common to all these forms

of HF. Finally, circulating hs-TnT and NT-proBNP levels are increased in chronic kidney disease (CKD), because of neurohormonal activation associated with CKD, and contributing to cardiac damage,[32] and because of reduced renal clearance.[33] Nonetheless, hs-TnT retains independent prognostic value from NT-proBNP across all eGFR ranges. The best hs-TnT and NT-proBNP cut-offs tend to increase with declining renal function, but patient categorization according to these cut-offs results very effective for risk stratification. Indeed, patients with both biomarkers higher than or equal to the respective cut-offs have the worst prognosis, and those with both biomarkers below cut-offs have the better prognosis; furthermore, the condition of only one biomarker ≥cut-off, denoting a moderate severity of ongoing myocardial damage, is associated with an intermediate prognosis.

A recent study confirmed the independent prognostic value of hs-troponin assays (both T and I) compared to NT-proBNP in patients with either LVEF <50% or ≥50%, thus corroborating our conclusions, although in a much smaller population (n=1096), and with a shorter follow-up duration.[34] Notably, both median levels and AUC-defined hs-TnT cut-offs were higher than those we are reporting, possibly reflecting different inclusion criteria or the specific ethnic group assessed (61% Chinese patients, 27% Malay patients).[34] On the other hand, the consistency of the main results, i.e. that hs-TnT refines risk stratification when added to NT-proBNP, and that hs-TnT cut-offs close to the upper reference limit are discriminator of prognosis, provide strong conceptual support to the combined assessment of NT-proBNP and hs-TnT for risk stratification of patients with chronic HF. In particular, the hs-TnT assay is commonly available because of its established role in the diagnosis and management of acute coronary syndromes.[35] The assay has been extensively validated, has limited costs, and is automated, allowing to reduce human workload and sample processing times.[29] Finally, result interpretation is straightforward, especially since the 18 ng/L cut-off holds independent prognostic significance in the whole population, as well as in categories identified by patient sex, HF etiology, and eGFR classes (as demonstrated in our previous meta-analysis).[6] Overall, the hs-TnT assay seems to meet the prerequisites for widespread diffusion for risk stratification of stable chronic HF patients,[36] although dedicated

analyses should explore the balance between increased costs and prognostic benefit from combined NT-proBNP and hs-TnT evaluation.

In the search for a multi-marker strategy for chronic HF, many circulating molecules have been evaluated in addition to natriuretic peptides and troponins. Among them there are soluble suppression of tumorigenesis-2 (sST2),[9,37] galectin-3,[10] growth-derived factor-15 (GDF-15),[10] and hs-CRP as an indicator of inflammation. In particular, in the Val-HeFT cohort (included in our population), a relationship between hs-CRP quartiles and mortality was observed, the prognostic power of hs-CRP being independent of HF etiology and BNP.[38] In a small study on advanced chronic HF, not included in the meta-analysis because of no available individual patient data, hs-CRP was predictive over both NT-proBNP and hs-TnT.[10] In the present analysis, the majority of studies reporting data on hs-TnT considered also NT-proBNP and hs-CRP. This biomarker of inflammation was not an independent predictor of outcome or improved prognostic performance over hs-TnT plus NT-proBNP, possibly because of the link between myocardial necrosis and inflammation, reflecting in overlapping prognostic information. The same conclusion applied to several patient categories.

Renal dysfunction has been identified as a predictor of prognosis in chronic HF, as previously reported in terms of serum creatinine >176 μmol/L,[39] lower creatinine clearance,[40] or lower eGFR.[12] Herein, we confirm that eGFR holds independent prognostic significance from NT-proBNP and hs-TnT. Furthermore, we report that patient categorization according to NT-proBNP and hs-TnT has strong prognostic significance across eGFR categories in chronic HF.

The present study is based on the data repository created for the meta-analysis on hs-TnT in chronic HF, and does not include papers published after April 2017, which are basically limited to a study presented in the Discussion, and which stands in agreement with our conclusions.[34] Because of limitations related to data collection, only NT-proBNP was evaluated, although the assessment of BNP would be interesting as well. The impact of comorbidities and drug or device therapies on the prognostic relevance of biomarkers remains to be elucidated, and the specific

setting of patients on dialysis was not evaluated. Furthermore, repeated biomarker evaluations were not considered, albeit potentially useful in order to further refine prognostic stratification. Finally, as stated above, dedicated studies should assess the cost-efficacy balance of a multi-marker assessment in HF outpatients.

In conclusion, hs-TnT conveys prognostic information that is independent from NT-proBNP, while hs-CRP does not. Concomitant assessment of eGFR may further refine risk stratification. The best hs-TnT and NT-proBNP cut-offs for the prediction of all-cause death increased progressively with declining renal function. Patient categorization according to these cut-offs helped predict all-cause and cardiovascular mortality and cardiovascular hospitalization across the whole range of renal function.

Conflict of Interest Disclosures

Dr. Januzzi has received grant support from Siemens, Singulex, and Prevencio; consulting income from Roche Diagnostics, Critical Diagnostics, Sphingotec, Phillips, and Novartis; and participates in clinical end point committees for Novartis, Amgen, Janssen, and Boehringer Ingelheim. Dr. Latini and Dr. Masson have received grant support and travel reimbursements from Roche Diagnostics. Dr. Tavazzi reports personal fees from Servier, personal fees from CVIE Therapeutics, outside the submitted work. Dr. Gravning reports lecture fees from AstraZeneca, Siemens and Abbott Laboratories, outside the submitted work. Dr. Brunner-La Rocca reports unrestricted research grants and consulting fees from Roche Diagnostics, as well as unrestricted research grants from Novartis and GlaxoSmithKline outside this work. Dr. Bayes-Genis has received grant support from Roche Diagnosis, lecture honoraria from Roche Diagnostics and Critical Diagnostics, and consulting income from Roche Diagnostics, Critical Diagnostics, and Novartis. Dr Lupón has received lecture honoraria from Roche Diagnostics. Dr. de Boer reports that Roche, Novartis, and AstraZeneca offered consultancy to UMCG; he also reports grants from AstraZeneca, grants from Bristol Myers Squibb, and grants from Trevena, outside the submitted work. Dr. Gustafsson reports personal fees from Boehringer-Ingelheim, personal fees from Novo Nordisk, personal fees from Novartis, personal fees from MSD, personal fees from Astra-Zeneca, outside the submitted work. Dr. Gaggin has received grant support from Roche and Portola; consulting income from Roche Diagnostics, Amgen and Ortho Clinical; research payments for clinical endpoint committees for EchoSense and Radiometer. Dr Eggers has received honoraria from Abbott Laboratories and AstraZeneca, and has served as a consultant for Abbott Laboratories and Fiomi Diagnostics. Dr. Tang reports grants from National Institutes of Health, outside the submitted work. All disclosed relationships are modest. All other Authors have nothing to disclose.

Figure legends

Figure 1. Biomarkers and prognosis in heart failure.

Areas under the curve (AUC) for N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hs-TnT), hs-C-reactive protein (hs-CRP), and their combination are represented. All biomarkers were log_2-transformed. As reported in the text, p values for hs-TnT vs. either NT-proBNP or hs-CRP were both <0.001; hs-TnT vs. (hs-TnT+NT-proBNP+hs-CRP), p<0.001 for all-cause and cardiovascular (CV) death, p=0.005 for cardiovascular hospitalization.

Figure 2. Biomarker-based categorization for predicting all-cause mortality.

eGFR, estimated glomerular filtration rate (expressed as mL/min/1.73 m^2); NT, N-terminal fraction of pro-B-type natriuretic peptide; TnT, (high-sensitivity) troponin T. The numbers of patients at risk is reported in **Supplemental Table 7**.

Figure 3. Biomarker-based categorization for predicting cardiovascular mortality.

eGFR, estimated glomerular filtration rate (expressed as mL/min/1.73 m^2); NT, N-terminal fraction of pro-B-type natriuretic peptide; TnT, (high-sensitivity) troponin T. The numbers of patients at risk is reported in **Supplemental Table 7**.

Figure 4. Biomarker-based categorization for predicting cardiovascular hospitalization.

eGFR, estimated glomerular filtration rate (expressed as mL/min/1.73 m^2); NT, N-terminal fraction of pro-B-type natriuretic peptide; TnT, (high-sensitivity) troponin T. The numbers of patients at risk is reported in **Supplemental Table 7**.

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